REMARKS

Claim Amendments

Applicants have cancelled claims 8-52 without prejudice and disclaimer. These claims were withdrawn from consideration as a consequence of a restriction requirement. Applicants reserve the right to prosecute these claims in one or more divisional applications.

In addition, applicants propose to add new Claims 53-56. Claim 1 and Claim 2 both recite a two-member Markush group, and Claims 53/54 and 55/56 depend from Claims 1 and 2, respectively, and recite each of the two members of the Markush group. Applicants respectfully submit that these new Claims are fully supported by the original specification as filed, and do not raise any issues of new matter or patentability. Entry of the new claims and favorable reconsideration are respectfully requested.

Claim Rejections

Applicants acknowledge the withdrawal of all rejections under 35 U.S.C. § 112, and indication that the invention with respect to NZ10 is both novel and nonobvious. Accordingly, applicants respectfully submit that new claims 54 and 56 are allowable.

The Office Action, however, maintains that the claimed methods with respect to ORFV2-VEGF are obvious over Lyttle *et al.* in view of Thomas *et al.* Applicants respectfully traverse and request reconsideration and withdrawal of the rejection.

Lyttle *et al.* purports to disclose that the genome of the NZ2 strain of the orf virus shares some sequence homology to mammalian VEGF genes, and that supernatants from cultured cells infected with the NZ2 virus are mitogenic for vascular endothelial cells. The Office Action alleges that this, in view of Thomas, which teaches that mammalian VEGF stimulates proliferation of endothelial cells, renders obvious the claimed invention which recites a method for

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stimulating proliferation of endothelial or mesodermal cells using an effective amount of ORFV2-VEGF.

Applicants respectfully submit that the above allegation is improper for the following reasons. First of all, Lyttle *et al.*, even combined with Thomas *at al.*, at most provides an "obvious to try" argument for testing if the product of a viral gene that shares some sequence homology with the VEGF family of genes may have similar activities. The references, however, fail to provide any reasonable expectation of success.

The Office Action concedes that sequence homology alone does not reasonably predict that similarity in activities exists, but asserts that Lyttle *et al.* suggested both sequence homology and activity characteristic of VEGF. However, Lyttle *et al.* did ***not*** suggest that the observed activity in the cell supernatant was due to a viral *protein*. In this regard, the Office Action misquoted Lyttle *et al.*, because at page 91, Lyttle *et al.* only stated that "it seems likely that that the response is a direct effect of the activity of the VEGF-like ***gene***," not a VEGF-like ***protein***. In fact, Lyttle *et al.* did not disclose, or even suggest that there existed an ORFV2-VEGF protein or peptide in the cell supernatant, not to mention its activity. As is well known to an ordinarily skilled person in the art, cell supernatant is the fluid phase that remains after centrifugation of a cell homogenate at high speed and contains all soluble components of the cell, including many host proteins. As indicated in applicants' response to the previous Office Action, the paragraph in Lyttle *et al.* concerning the alleged stimulating activity merely compares the supernatant from infected cells to that from non-infected cells, and is based on some unpublished data with no experimental details.

Significantly, in Lyttle *et al.* there is no teaching or suggestion that the difference was due to a viral protein, to say nothing about the particular ORFV2-VEGF peptide at issue. An ordinarily skilled person in the art will recognize that any assertion based on unpublished data cannot and should not be relied upon. Even if such an assertion is given weight, many equally viable

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possibilities exist to explain the difference in the activities between the two types of cell supernatants. For example, it is well understood that many host genes will express differently after a viral infection. Thus, the difference in stimulating activity may be due to the altered expression level of a host gene or genes in response to the viral reaction. Alternatively, the difference may be due to an expressed viral protein that is not the product of the ORFV2-VEGF gene. Even if it is possible that the ORFV2-VEGF gene is expressed and is a directly responsible for the activity difference, it is likely that the active protein may be a result of post-transcriptional and/or post-translational modifications. The discussion in Lyttle *et al.* hypothesizes on how VEGF activity might be an advantage to the virus and explicitly states that the reason for any observed pathology is **not clear**. This admission by Lyttle et al. is clear evidence that a person of ordinary skill in the art could not have had a reasonable expectation that the observed activity in the supernatant was attributable to the ORFV2-VEGF protein.

In any event, there is no basis to ascertain, from the two or three sentences in Lyttle *et al.*, referring to some unpublished data with no experimental detail, that the ORFV2-VEGF protein, in and of itself, would be effective in stimulating proliferation of endothelial or mesodermal cells. Furthermore, such a deficiency was not and cannot be corrected by the Thomas reference, which merely discloses the activities of VEGF proteins.

In other words, Lyttle *et al.*, even if combined with Thomas *et al.*, does not provide the legally required reasonable expectation of success for the claimed invention. Perhaps it was "obvious to try," if that, but given the numerous possibilities and unpredicatability of the art, no reasonable expectation of success existed to an ordinarily skilled artisan. As a proof of applicants' invention to applicants' peers, applicants' data and conclusion related to the claimed invention are published in a highly prestigious, peer-reviewed scientific journal. *See* Wise *et al.*, 1999, Proc. Nat'l Acad. Sci. 271:5638-46.

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Secondly, applicants respectfully submit that the rejection of claim 2 and claims dependent therefrom is especially improper and should be withdrawn. This is because the finding that ORFV2-VEGF binds to VEGFR-2 is highly unexpected.

ORFV2-VEGF is unique among the VEGF family of proteins in its receptor recongnition profile, in that it recognizes only VEGFR-2, but not VEGFR-1 or VEGFR-3, *See* Wise *et al.*, supra, (page 3075, text bridging the right and the left columns). Prior to the present invention, structural analyses of the VEGF family of proteins had identified residues on the proteins that were believed to be ***conserved and important*** for binding to VEGF receptors. See e.g. Keyt *et al.*, (1996), J. Biol. Chem. 271:5638-5646 (copy attached for Examiner's convenience). In this regard, certain residues on the VEGR proteins were believed to be critical and conserved for binding to VEGFR-1 and others critical for binding to VEGFR-2. Based on its primary sequence, ORFV2-VEGF was expected to bind to VEGFR-1. However, it was surprisingly found to bind to VEGFR-2. This suggests that the mechanism of ORFV2-VEGF in binding to VEGF receptors, and perhaps its mechanism in activating downstream stimulation events are quite different from other VEGF proteins. See Wise *et al.*, supra.

In short, the ability for ORFV2-VEGF to bind and activate only VEGFR-2 is unique and surprising. Consequently, methods using ORFV2-VEGF for activating VEGFR-2 are not obvious over the prior art, and the obviousness rejection should be withdrawn.

Because Lyttle *et al.* and Thomas *et al.* fail to teach or suggest a method for stimulating proliferation of endothelial or mesodermal cells via exposing the endothelial cells to an effective amount of an ORFV2-VEGF polypeptide,, these prior art references do not render claims 1-7 and new claims 53-55 obvious. Accordingly, applicants respectfully request reconsideration and allowance of all pending claims.

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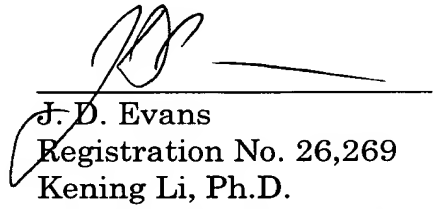
If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #1064/44803).

Respectfully submitted,

February 19, 2002



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